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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/570,046	04/17/2006	Toshikazu Nakamura	2006_0233A	8161

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WENDEROTH, LIND & PONACK, L.L.P.
1030 15th Street, N.W.,
Suite 400 East
Washington, DC 20005-1503

EXAMINER	
ALLEN, MARIANNE P	
ART UNIT	PAPER NUMBER
1647	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/570,046	NAKAMURA ET AL.	
	Examiner	Art Unit	
	Marianne P. Allen	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 January 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4,5,8-10,13-17,20,21 and 24-52* is/are pending in the application.

4a) Of the above claim(s) *1,4,5,8-10,13-17,20,21 and 24-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *28-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1, 4-5, 8-10, 13-17, 20-21, and 24-52* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 1/21/09 has been entered.

Claims 2-3, 6-7, 11-12, 18-19, and 22-23 have been cancelled. Claims 28-52 have been newly added.

Applicant's arguments filed 1/21/09 have been fully considered but they are not persuasive.

Claims 28-52 are under consideration by the examiner.

Election/Restrictions

Claims 1, 4-5, 8-10, 13-17, 20-21, and 24-27 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 11/21/07.

Claim Objections

Applicant is advised that should claims 30, 38, and 46 be found allowable, claims 35, 43, and 51, respectively, will be objected to under 37 CFR 1.75 as being a substantial duplicate

thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

Each set of claims is directed to the same method. A drug that further comprises a gelling agent will be a drug in the form of a gel.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 28-52 have been newly introduced.

Basis is not seen for the limitation promoting "enhanced wound healing." Original claims 9-12 were directed to methods for treating a skin ulcer, promoting neovascularization, and promoting granulation formation. The specification does not disclose nor define what constitutes "enhanced wound healing." It is not clear what biological effects are required by the claims. This concept does not appear to have been contemplated by the originally filed specification.

Basis is not seen for the step of "selecting a mammal having a skin ulcer." The specification does not disclose any selection criteria. This concept does not appear to have been contemplated by the originally filed specification.

Basis is not seen for the step of "analyzing the formation of granulation tissue." The specification does not disclose any methods of analysis for a mammal being treated. The only granulation analysis disclosed involved stained tissue sections that had been removed from an experimental animal. This concept does not appear to have been contemplated by the originally filed specification.

With respect to claims 45-52, the claims do not make clear how the drugs of claims 46-52 are topically administered if the skin has already been contacted with the wound covering agent. The specification does not disclose the recited wound covering agents in combination with the formulations of claims 46-52, in particular ointments, creams, and fatty acid esters. Basis is not seen for the step of "providing a wound covering agent." The specification does not disclose manufacturing wound covering agents nor any selection criteria for choosing a particular wound covering agent. Finally, it is noted that these claims are not limited to sealing-type wound covering agents which provide a wet environment at a wound part and can permeate oxygen and water steam without permeating liquid and bacteria.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 28-30, 33-38, and 41-44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toyoda et al. in view of Seki et al., Nakamura et al. (U.S. Patent No. 5,342,831), Nakamura et al. (EP 461,560 A1), and Yoshida et al. (Journal of Investigative Dermatology), and either Morishita et al. (U.S. Patent No. 7,247,620) or Morishita et al. (WO 02/089854).

Toyoda et al. discloses that overexpression of HGF in transgenic mice promotes granulation. Increased presence of HGF protein is determined by using antibodies. Toyoda discloses topical or local administration of HGF to skin wounds to promote healing and granulation formation. The reference specifically suggests using HGF to treat refractory skin ulcers from various diseases. See page 99, right column, last paragraph, as well as abstract; pages 96-97 and 100, section 3.5, and Figures 2 and 5. Toyada et al. does not disclose the HGF of SEQ ID NO: 1.

Seki et al. discloses the HGF of SEQ ID NO: 1. This naturally occurring variant has the same biological activities as the HGF retaining the five amino acids (SEQ ID NO: 3). The variant still binds antibodies to HGF. See at least abstract and pages 323 and 325-326.

Nakamura et al. (U.S. Patent No. 5,342,831) discloses using HGF to treat skin ulcers (dermoulcers). Methods of administration, formulations, and dosages are disclosed. Gels, lotions, ointments, and aqueous solutions are disclosed. See at least column 2, lines 50-68, and column 5, lines 50-63.

Nakamura et al. (EP 461,560 A1) discloses the HGF of SEQ ID NO: 1. This naturally occurring variant has the same biological activities as the HGF retaining the five amino acids (SEQ ID NO: 3). See at least column 20, claims, and Figure 15.

Yoshida et al. discloses that inhibiting the action of HGF protein by using antibodies can suppress or inhibit granulation tissue formation. See at least abstract.

Morishita et al. (U.S. Patent No. 7,247,620) discloses treating diabetic skin ulcers by topical administration of the HGF gene to promote granulation. There is increased presence of HGF protein in the healing wound. (See at least abstract, claims, and column 3, lines 5-20; columns, 9-10, particularly column 10, lines 1-5 and 41-45; and columns 17-18.) Morishita et al. (WO 02/089,854) is the PCT from which the '620 patent originated and has an equivalent disclosure.

It would have been obvious to substitute the HGF variant of SEQ ID NO: 1 as taught by Seki et al. and Nakamura et al. (EP 461,560 A1) to treat diabetic skin ulcers as suggested by Moroshita et al., Nakamura et al. (U.S. Patent NO. 5,342,831) and Toyoda et al. With respect to Toyada et al., one of ordinary skill in the art would have appreciated that refractory ulcers

include diabetic skin ulcers. This would have been a known complication of diabetes. Morishita et al. specifically disclose treating diabetic skin ulcers. One would have been motivated to do so as Toyoda et al. and Moroshita et al. both disclose that HGF protein promotes granulation and Yoshida et al. discloses that inhibiting the action of HGF protein by using antibodies can suppress or inhibit granulation tissue formation. Based on the teachings of Nakamura et al. ('560) and Seki et al., one of ordinary skill in the art would have expected the HGF variant of SEQ ID NO: 1 to have this biological activity.

With respect to Morishita et al. (U.S. Patent No. 7,247,620), applicant cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 CFR 1.55. See MPEP § 201.15.

With respect to the limitation "selecting a mammal having a skin ulcer," the claims do not set forth any particular criteria for selection. As such, the fact that a subject with an ulcer is treated is sufficient to meet this limitation.

With respect to the limitation of "analyzing the formation of granulation tissue," the claims do not set forth any particular method of analysis. As the goal of the prior art is to promote granulation formation and heal wounds, successful treatment as taught by the prior art is sufficient to meet this limitation.

Applicant's arguments chiefly concern the proposition that one of ordinary skill in the art would not have expected HGF with a five amino acid deletion (dHGF or the instant SEQ ID NO:

1) to have a biological effect the same or similar to an HGF without this deletion. This is not persuasive. While the art applicant references discloses some structural and functional differences between the two forms, this art establishes that dHGF binds to the receptor and causing signaling through the receptor, resulting in a biological effect comparable to the intact HGF. All of the differences commented on by applicant would have been known to those of ordinary skill in the art. This knowledge would have informed one as to how to modify a dHGF preparation (for example to compensate for the level of heparin binding, degree of solubility, or the mitogenic activity level) but **would not** have led one of ordinary skill in the art not to use the dHGF of SEQ ID NO: 1. In particular, Ozeki et al. (2006) is not germane as it was published well after the effective filing date relied upon by applicant. Otsuka et al. (2000) and Lindsey et al. (2002) are not germane as they discuss deleted forms of HGF that are not within the scope of the claims. That is NK1, NK2, and NK4 are largely truncated HGF proteins that act as **antagonists**. Although Lindsey et al. discusses NK1 and NK2 mutants also having the five amino acid deletions (dNK1 and dNK2), the results disclosed are for endometrium and not skin ulcers. Again, these proteins **do not** lack the biological activity of the undeleted form. With respect to the various mutants of Kinosaki et al. (1998), it is noted that most of the alananine scanning mutants were biologically active. See Figures 2A and 2B. The reference presents evidence that dHGF was biologically active. See Figure 4. While there may be some differences in heparin binding, the claims and disclosure do not require heparin binding activity for granulation formation or wound healing. Likewise, Shima et al. (1994) demonstrates that dHGF was mitogenic. See Figures 1 and 2.

It is not unexpected that deletion mutants differ in structure. After all, a deletion mutant by definition has a different structure. It is not unexpected that there is some change in degree or kind of function. However, applicant has not established that the five amino acid deletion present in SEQ ID NO: 1, a known deletion mutant, resulted in any activity change that would have lead one of ordinary skill in the art to doubt that the known effect of HGF in granulation formation or enhancing wound healing would not be present in dHGF. The claims do not require a particular degree of activity or mechanism of action. To the degree that applicant may be arguing unexpectedly better results between HGF having the five amino acid deletion and intact HGF, no such results have been shown. There is no comparison of granulation formulation caused by the dHGF of SEQ ID NO: 1 or intact HGF.

Claims 28, 30-31, 35-39, 43-47, and 51-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Toyoda et al. in view of Seki et al., Nakamura et al. (U.S. Patent No. 5,342,831), Nakamura et al. (EP 461,560 A1), and Yoshida et al. (Journal of Investigative Dermatology), and either Morishita et al. (U.S. Patent No. 7,247,620) or Morishita et al. (WO 02/089854) and further in view of De Busk et al. (U.S. Patent Publication 2004/0001878).

Toyoda et al., Seki et al., Nakamura et al. (U.S. Patent No. 5,342,831), Nakamura et al. (EP 461,560 A1), Yoshida et al. (Journal of Investigative Dermatology), Morishita et al. (U.S. Patent No. 7,247,620), and Morishita et al.are applied as above. They do not disclose the inclusion of an antiseptic nor the wound covering agents recited in claim 45.

De Busk et al. discloses using hydrocolloid dressings to treat skin ulcers and promote granulation formation. Antiseptics can be included with the treatment drug. Gels and liquids are disclosed for administration. See at least abstract, claims, and paragraphs [040, 045, 078].

It would have been obvious to use a wound covering agent such as those taught by DeBusk et al. with dHGF to treat a skin ulcer as suggested by the prior art as set forth above. Wound covering agents would have been routinely used to treat skin ulcers and the cited prior art suggests using dHGF for this purpose.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is (571)272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa